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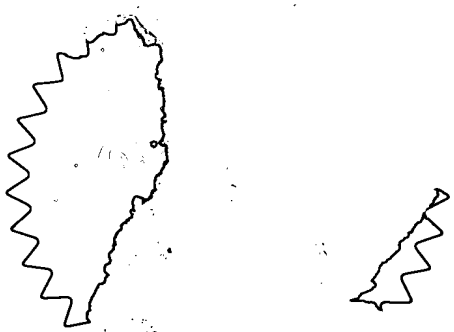

Signed P. Mahoney

Dated 04 MAY 2001

GB9823246.5

By virtue of a direction given under Section 3 of the Patents Act 1977, the application is proceeding in the name of

WEST PHARMACEUTICAL SERVICES DRUG DELIVERY & CLINICAL RESEARCH CENTRE LTD,
Incorporated in the United Kingdom,
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[ADP No. 07657521001]

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1. Your reference

DANR\P19614GB

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3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Danbiosyst UK Ltd
Albert Einstein Centre
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Nottingham NG7 2TN
United Kingdom

Patents ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation

United Kingdom

6496178 001

4. Title of the invention

A NASAL DRUG DELIVERY COMPOSITION

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

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Patents ADP number *(if you know it)*

1305010

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

| Country | Priority application number *(if you know it)* | Date of filing *(day / month / year)* |
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7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

| Number of earlier application | Date of filing *(day / month / year)* |
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8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

*a) any applicant named in part 3 is not an inventor, or*
*b) there is an inventor who is not named as an applicant, or*
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| Description | 7 |
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| Priority Documents | 0 |
| Translations of priority documents | 0 |
| Statement of inventorship and right to grant of a patent *(Patents Form 7/77)* | NO |
| Request for preliminary examination and search *(Patents Form 9/77)* | NO |
| Request for substantive examination *(Patents Form 10/77)* | NO |
| Any other documents *(please specify)* | |

11. I/We request the grant of a patent on the basis of this application.

Signature Eric Potter Clarkson Date

ERIC POTTER CLARKSON 23 October 1998

12. Name and daytime telephone number of person to contact in the United Kingdom 0115 9552211

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# A nasal drug delivery composition

This invention concerns a new composition and more particularly is concerned with a new composition for the improved delivery of drugs to the nose for systemic absorption. The invention is especially concerned with an emulsion formulation for poorly water soluble drugs that are given in a relatively high dose, such as analgesics, including non-steroidal anti-inflammatory agents, and anti-Parkinson drugs.

The nasal route of drug delivery affords rapid absorption of drugs into the blood circulation. In some cases the absorption of almost the whole dose can be achieved and the pharmacokinetics can be similar to intravenous administration. Such rapid and effective drug delivery can be useful in the treatment of crisis situations such as pain (to include breakthrough pain, headache) migraine, convulsions, impotence, nausea, etc. Nasal formulations for the delivery of analgesic agents such as morphine, butorphanol, fentanyl, buprenorphine have been described. For a review see Nasal Systemic Delivery, Eds. Chien et al. Dekker, New York, 1987.

The non-steroidal analgesics (NSAID) such as the cyclooxygenase (COX) COX-1 and COX-2 inhibitors have an important role in pain management. Compounds include ibuprofen, flurbiprofen, diclofenac, indomethacin, piroxicam, ketoprofen, etodolac, diflusinal, meloxicam, aceclofenac, fenoprofen, naproxen, tiaprofenic acid, tolmetin. Such drugs are normally given by mouth for absorption from the gastrointestinal tract but can also be given by other routes to include injection.

Nasal delivery of poorly soluble drugs that need to be given in a relatively high dose is often problematic. The maximum volume to be given in each nostril is 100-125 µl and with a low solubility of the drug it is normally not possible to achieve a simple solution formulation.

The nasal delivery of drugs such as analgesics to include non steroidal anti inflammatory drugs and drugs for Parkinson's disease is therefore problematic. The dosages are often high, the drugs have limited water solubility and the compounds can be be irritant to mucosae. It is known that solutions of NSAIDs at relatively high concentrations can be prepared by use of certain salt forms eg. (K+) or by adjustment of pH. The osmolarity of such solutions can readily exceed isotonicity and as a consequence be irritant.

We have found that the effective nasal delivery of poorly soluble drugs such as analgesics (to include NSAIDS), and drugs for Parkinson's disease and the treatment of impotence can be achieved using a two phase system such as an oil-in-water emulsion, that demonstrates a reduced nasal irritation.

The use of non-steroidal anti-inflammatory drugs (eg. paracetamol, diclofenac or ibuprofen for the treatment of nasal polyps, chronic rhinosinusitis or anosmia is described in WO9703659. There is no suggestion that the nasal route can be used for the systemic delivery of NSAIDs nor is there a description of two phase systems such as an emulsion for this purpose.

The nasal administration of Ketorolac (US patent 4089,969), for analgesic and anti-inflammatory activity has been described in EP0524587. Formulations based on concepts of bioadhesion such as cellulose gums and block copolymers, as well as formulations containing enhancing agents were described. The use of an emulsion formulation was not described.

The nasal delivery of NSAIDs and analgesics to the systemic circulation using small bioadhesive microspheres and active drug has been described in US5707644. There is no suggestion that a liquid formulation comprising a two phase system such as an emulsion could be used.

Oil in water emulsion systems for the improved delivery of drugs via the nasal route have been described previously. Ko et al (J. Microencaps. 15, 197, 1998) administered testosterone to rabbits. The drug was dissolved in soybean oil. Karali et al (Pharm. Res. 9,. 1024, 1992) used an oleic acid mono-olein emulsion to deliver a lipid soluble renin inhibitor. The emulsion was effective because it contained membrane modifying adjuvants. The use of castor oil was not disclosed.

The potential use of emulsion systems for the nasal delivery of nicotine is described in WO9312764 and GB2133691. However, the teaching of these two patents is to the use of systems of a defined viscosity. An oily emulsion is mentioned simply as a formulation option.

Amphotericin containing emulsions and lyophilised counterparts, based on soybean oil as the oily phase, have been described in JP4173736 for use as nasal drops. It is well known that in such emulsions the drug is intercalated into the surface layer of the emulsion and is not dissolved in the oily phase (Davis et al. Ann N.Y. Acad. Sci. 507, 75, 1987).

The local treatment of nasal disorders using drugs dissolved in the oily phase of an emulsion is described in JP5124965. The oil phase was soybean oil and the drugs were steroid and steroid derivatives. Similarly the sustained release nasal drops containing vasoconstrictor and antihistamines in an oil in water emulsion are described in JP7258069 for local effect.

Emulsion vehicles have also been used to improve the nasal delivery of polar drugs such as peptides and as vaccine adjuvants. In such formulations the drug is not dissolved in the oil phase of the emulsion but can be adsorbed to the surface of the emulsion droplets (WO9511700, US5514670, WO9305805, US5716637. Emulsions may also be used in order to disperse absorption promoting agents such as phospholipids as US5179079.

In none of these prior art examples have oil in water emulsions based on a hydroxylated vegetable oil such as castor oil been used for the nasal administration of drugs in order to provide solubilisation of the therapeutic agent and reduced nasal irritation.

We have found surprisingly that it is possible to deliver poorly water soluble drugs to the nasal mucosa for subsequent delivery to the systemic circulation by emulsion formulations containing castor oil as the oil phase. By a poorly water soluble drug we mean a drug with a solubility in water less than 10 mg/ml at pH 7.4 at 25°C. By a relatively high dose of drug we mean more than 1 mg of drug.

According to the present invention there is provided a Pharmaceutical comprising a oil in water emulsion and a drug dissolved in the emulsion wherein the oil composition phase comprises a hydroxylated vegetable oil. By hydroxylated vegetable oil we mean an oil such as castor oil that consists of the glycerides of riconoleic, isoriconoleic acid, both being hydroxy fatty acids.

The poorly water soluble drug is preferably largely contained within the oil phase of an oil in water emulsion. By the term preferably largly is the oil phase we mean that more than one half of the available drug is dissolved in the oil phase and preferably more than 75% of the available drug is to be found dissolved in the oil phase. We have found surprisingly that the hydroxylated oil, castor oil can give a high solubility for poorly water soluble drugs so that a therapeutically relevant dose can be delivered via the nose wherein the drug is contained in a liquid formulation. Moreover, as a second aspect of the present invention, again surprisingly, is that the emulsion formulation can greatly reduce any irritation associated with the drug. Without wishing to be bound by any theory, it is believed that such reduction in irritation is due to the fact that the drug is dissolved largely in the oil phase, since it is the drug in the aqueous phase that can lead to irritation of the nasal mucosa.

By castor oil we include ricinus oil, oil of Palma Christie, tangantargon oil and Neoloid as described in the Merk Index 12th Edition p. 311. Castor oil is a fixed oil usually obtained by the cold pressing of the seeds of Ricinus Communis L., (Fam. Euphorbiaceae). The fatty acid composition is stated in the Merk Index to be 87% ricinoleic acid, 7% oleic acid, 3% linoleic acid, 2% palmitic acid, 1% srearic acid and dihydroxystearic acid in trace amounts.

We also include the oil from Ricinus Zanzibarinus in our definition of Castor oil. This oil also has a high content of glycerides of ricinoleic acid (Evans, in Trease and Evans, Pharmacognosy, 13th Edition, Bailliere Tindall, London 1989, P. 333.

The special role of castor oil could be due to the fact that it contains hydroxylated fatty acids. Conventional vegetable oils such as soy bean oil, cotton seed oil, arachis oil used for the preparation of pharmaceutical emulsions which will be familiar to the person skilled in the art, do not demonstrate such good drug solubility.

The oil phase in the emulsion can constitute from 1 to 50% v/v. A preferred concentration of oil in the emulsion is from 10 - 40% v/v and more preferably 20 - 30% v/v.

The emulsions for nasal delivery can be prepared by conventional methods such as homogenisation of a mixture of the oil and an aqueous phase together with a stabilizing agent. The microfluidiser or ultrasonic device can be used; the former is preferred for large scale production. The stabiliser can be a pharmaceutically acceptable material such as a phospholipid (eg. egg or soy lecithin) or a block copolymer such as poloxamer 188, suitable for parenteral administration. Egg or soy lecithin are preferred emulsifiers. The concentration of emulsifier can be from 0.1 to 10% w/v in the aqueous phase of the emulsion but more preferably from 1 - 5% w/v concentration.

The nasal administration of drugs may provide a direct access to sites of analgesic action such as the cerebrospinal fluid and the nervous ganglia associated with conditions such as migraine. Consequently the required dose of an NSAID administered nasally can be less than that required when given by the usual oral route. It is also known that the nasal route can be used to avoid metabolism in the liver, although there are enzymes in the nasal cavity that can degrade drugs.

Hence, a wide variety of drugs can be included in a nasal emulsion based on an oil such as castor oil. These drugs not only include analgesic agents, drugs for the treatment of Parkinsons disease, but also drugs for the administration of drugs where rapid onset of action may be required; for example nausea and vertigo, convulsions, panic attacks, cardiac problems, impotence, erectile dysfunction, migraine, sedation (particularly in children), withdrawal symptoms. Drugs can include nicotine, bezodiazapines, midazolam, diazepam, diamorphine, cannabinoids.

The fact that for some drugs most of the therapeutic agent is dissolved in an oil phase and not in contact with water will also help improve the stability of the drug in the formulation.

The loading of the drug in the emulsion will be determined by the dose of the drug required for a therapeutic effect and the solubility of the drug in castor oil. Doses of 10mg to 100mg could be administered. Some drugs may be oily in nature and thereby be miscible with the castor oil.

It will be clear to the person skilled in the art that additional formulation components can be added to the emulsion. These could include agents that promote the transmucosal absorption of drugs which as surfactants, bile salt, phospholipids as well as thickening agents and gelling agents that will serve to retain the formulation in the nasal cavity for an extended period of time. Such agents include cellulose polymers and in particular sodium carboxymethyl cellulose, alginates, gellans, pectins, acrylic polymers, agar-agar, gum tragacanth, gum xanthan, hydroxyethyl cellulose, chitosan, as well as block copolymers of the poloxyelthylel-polyoxpropylene class known as the poloxamers and poloxamines. Preservative agents could also be added such as methyl parabenzoates, benzylalcolol, chlorobutanol.

The emulsion can be administered to the nasal cavity using a conventional spray device. This can be a unit dose or multiple dose system. Such devices can be obtained from companies such as Pfeiffer and Valois.

**Example 1 Solubility of flurbiprofen in vegetable oils**

The solubility of flurbiprofen in different vegetable oils was measured by the addition of increasing quantities of the drug to an oil system and determination of the maximum amount that will dissolve by observation of the resultant solution and the onset of a cloudy nature or precipitation. The solubility of flurbiprofen (obtained from The Boots Co. Ltd.) at room temperature measured in this way was less than 50 mg/ml mg/ml in soybean oil BP (obtained from Kahlshams, Sweden) and 150 mg/ml in castor oil BP (William Ransom, UK).

**Example 2**

An oil in water emulsion containing 45 mg/ml flurbiprofen and a 30% v/v oil phase was prepared as follows:

Approximately 60 ml of castor oil BP (William Ransom, UK) was warmed to 30-40°C and 11.25 g of flurbiprofen (Boots Co., UK) added and stirred to dissolve. The volume of the flurbiprofen solution was adjusted to 75 ml by adding further castor oil. Phosphate buffered saline (PBS) solution (pH 7.4) was prepared by dissolving a PBS tablet (Sigma, UK) in 200 ml of water. 150 ml of this solution was warmed to 40°C and 3 g of egg yolk lecithin

(Lipoid E80, Leopold, Germany) added and mixed to disperse. To the egg yolk phospholipid dispersion was added 4.2 g of glycerol (Boots Co. Ltd.). The glycerol was added to maintain isotonicity. This mixture was added to the flurbiprofen/castor oil solution and the two phases mixed using a Silverson L4R homogeniser, pulsed between speeds 5 and 10 for a period of 1 minute. This coarse emulsion was then passed three times through a Rannie Mini-Lab valve homogeniser at 10,000 psi to produce a milky off-white emulsion. The emulsion has a fine particle size (about 200 nm as measured using the method of photon correlation spectroscopy) and was stable on storage at room temperature. There was no evidence of separation of free oil nor drug crystals as viewed under the light microscope.

**Example 3 Irritation test in human**

In order to evaluate the relative irritancy of a solution and emulsion formulation of flurbiprofen two different formulations were evaluated.

*Solution formulation*:: Fluriprofen as the potassium salt at a concentration of 45 mg/ml was prepared by a process of simple dissolution in water administered using a Pfieffer multidose nasal device. A volume of 50 µl was administered into one nostril.

*Emulsion formulation:* An oil in water emulsion formulation as described in Example 2 containing 45 mg/ml of flurbiprofen was prepared and filled into a Pfieffer multidose nasal spray device. A dose of 50 µl was administered into one nostril.

One subject (female, age 50) tested each formulation on two separate occasions.

Irritancy was assessed using an analogue scale. The solution formulation based on the potassium salt of flubiprofen was noted as being irritant at a value of 10 on the irritancy scale.

The emulsion formulation was less irritant, being assessed as 4 on the irritancy scale.

**Example 4: Solubility of non-steroidal drugs in castor oil and soybean oil**

The solubility of additional NSAID drugs in the castor oil and soybean oil was measured at room temperature as in example 1. Ibuprofen, Indomethacin and naproxen (as obtained from Sigma Chemical Co.) were used. The results in Table 1 demonstrate the beneficial effect of a hydroxylated vegteable oil (namely castor oil) in improving drug solubility so that a nasal emulsion of low irritation can be formulated.

**Table 1**

**The solubility of ibuprofen, indomethacin and naproxen in castor oil (B.P) and soybean oil**

| Drug | Solubility in castor oil (mg/g) | Solubility in soybean oil (mg/g) |
|---|---|---|
| Ibuprofen | > 100 | >30 < 40 |
| Indomethacin | >15 < 20 | < 5 |
| Naproxen | >20 < 40 | < 10 |
| Apomorphine | >30 < 50 | < 10 |

## Claims

1. A pharmaceutical composition comprising an oil in water emulsion and a drug dissolved in the emulsion wherein the oil phase comprises a hydroxylated oil.

2. A pharmaceutical composition for nasal administration comprising an oil in water emulsion and a drug dissolved in the emulsion wherein the oil phase comprises a hydroxylated oil.

3. A composition comprising an oil in water emulsion and a drug dissolved in the emulsion wherein the oil phase comprise a hydroxylated oil for use in medicine.

4. A pharmaceutical composition comprising an oil in water emulsion and a drug dissolved in the emulsion for systemic delivery of a drug by the nasal route, where the oil phase comprises a hydroxylated oil.

5. A pharmaceutical composition according to Claims 1 - 4 where the hydroxylated oil in castor oil.

6. A composition according to Claim 1 - 5 where the drug is an analgesic agent or a drug for the treatment of Parkinson's disease or impotence.

7. A composition according to Claim 1 - 5 for the nasal administration of non-steroidal antiinflammatory (NSAID) agents to the nasal cavity.

8. A composition according to Claim 6 where the NSAID is flurbiprofen.

9. A composition according to Claim 6 where the NSAID is ibuprofen.

10. A composition according to Claim 6 where the NSAID is a COX-1 or COX-2 inhibitor.

11. A method for the rapid treatment of pain using an oil in water emulsion formulation containing a drug delivered by the nasal route.

12. A method according to Claim 11 where the drug is an NSAID.

13. The use of an oil in water emulsion in which the oil comprises castor oil and a drug in the manufacture of a medicament for nasal administration.

14. The use of an oil in water emulsion and a drug in the manufacture of a medicament for systemic delivery of the drug by the nasal route where the oil phase is said emulsion is a hydroxylated vegetable oil.

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FOR: **A NASAL DRUG DELIVERY COMPOSITION**

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SHEET NO. 1 OF 1